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EXAMINER	
JUNG, UNSU	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
06/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,608	BRUCHEZ ET AL.	
	Examiner	Art Unit	
	UNSU JUNG	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,7,10-13 and 16-45* is/are pending in the application.

4a) Of the above claim(s) *17-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,7,10-13,16 and 38-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendments in the reply filed on March 4, 2009 have been acknowledged and entered. The reply included amendments to claims 1, 12, and 42 and addition of new claims 44 and 45.

Status of Claims

2. Claims 1, 3, 4, 6, 7, 10-13, and 16-45 are pending, claims 17-37 have been withdrawn from consideration, and claims 1, 3, 4, 6, 7, 10-13, 16, and 38-45 are currently under consideration for patentability under 37 CFR 1.104.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The instant application filed on December 12, 2003, is a continuation-in-part of U.S. Patent Application Serial No. 09/972,744, filed on October 5, 2001, which in turn claims the benefit of U.S. Provisional Application Serial No. 60/238,677, filed on October 6, 2000, and U.S. Provisional Application Serial No. 60/312,558, filed on August 15, 2001.

Rejections Withdrawn

4. The following prior art rejections have been withdrawn in view of amended claims 1, 12, and 42 in the reply filed on March 4, 2009:

- Rejection of claims 1, 3, 4, 6, 7, 10-13, 16, 42, and 43 under 35 U.S.C. 103(a) as being unpatentable over Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018) in view of Rothbard et al. (U.S. Patent No. 6,495,663, filed on May 21, 1998); and
- Rejection of claims 38-41 under 35 U.S.C. 103(a) as being unpatentable over Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018) in view of Rothbard et al. (U.S. Patent No. 6,495,663, filed on May 21, 1998), and further in view of Foster et al. (U.S. Patent No. 4,444,879, Apr. 24, 1984) and Boguslaski et al. (U.S. Patent No. 5,420,016, May 30, 1995).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 45 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 45 contains the trademark/trade name NeutrAvidin™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe NeutrAvidin™ and, accordingly, the identification/description is indefinite.

New Grounds of Rejections

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 3, 4, 6, 7, 10-13, 16, and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018) in view of Rothbard et al. (U.S. Patent No. 6,495,663, filed on May 21, 1998) and Mixson (WO 01/47496 A1, published July 5, 2001 and filed December 20, 2000).

According to the specification on p14, lines 25-30, the terms "semiconductor nanocrystal," "quantum dot" and "Qdot™ nanocrystal" are used interchangeably herein to refer to semiconductor nanoparticles composed of an inorganic crystalline material that is luminescent (i.e., they are capable of emitting electromagnetic radiation upon excitation), and include an inner core of one or more first semiconductor materials that

is optionally contained within an overcoating or "shell" of a second semiconductor material.

Chan et al. teaches highly luminescent semiconductor quantum dots (semiconductor nanoparticles), which are biocompatible and are suitable for use in cell biology and immunoassays (see entire document, particularly Abstract). The advantages of using semiconductor quantum dots/ nanoparticles over the conventional organic fluorescent dyes are well known in the art. The advantages include resistance to photobleaching and enhanced quantum yield (p2017, Fig. 3 and 3rd column). The improved photostability of the semiconductor quantum dots/ nanoparticles would allow real-time observations of molecular trafficking in living cells (p2017, 2nd column, last paragraph). Further, sufficiently monodispersed semiconductor quantum dots/ nanoparticles would allow use in multiplex detection schemes (p2017, 2nd column, last paragraph).

With respect to claims 3 and 4, Chan et al. teaches a semiconductor nanoparticles comprising CdSe core (Fig. 1).

With respect to claims 6 and 7, Chan et al. teaches a semiconductor nanoparticles comprising ZnS shell (Fig. 1).

With respect to claims 12 and 13, Chan et al. teaches semiconductor nanoparticles comprising CdSe core and ZnS shell (Fig. 1).

However, Chan et al. fails to specifically teach a semiconductor nanoparticle complex, wherein the semiconductor nanoparticle is bound non-covalently to a plurality

of cationic polymers comprising of 5 to 25 contiguous Lysine (Lys) and/or Arginine (Arg) residues.

Rothbard et al. teaches methods and composition for transporting drugs and macromolecules across biological membranes wherein the biological membranes are contacted with a conjugate containing a biologically active agent that is covalently attached to a transport polymer (translocatable molecule, see entire document). Such transport polymer has 5 to 25 subunits of Lys or Arg (SEQ ID NO:'s 2, 3-11 and 13-17). The transport enhancing polymers are exemplified by peptides in which Lys or Arg residues constitute the subunits (SEQ ID NO:'s 2, 3-11 and 13-17). Exemplary eukaryotic cell membranes of interest include membranes of dendritic cells, epithelial cells, endothelial cells, keratinocytes, muscle cells, fungal cells, bacterial cells, plant cells and the like (column 3, lines 17-25). The conjugate is effective to enhance the transport rate of the conjugate across the biological membrane relative to the transport rate of the non-conjugate macromolecules along (column 6, line 63-column 7, line 5). Detecting uptake of macromolecules may be facilitated by attaching a fluorescent tag (see column 11, lines 3-4). Fluorescently labeled peptide polymers composed of 6 or more Arginine residues entered cells more efficiently than the tat sequence 49-57 in Fig. 1 (see column 11, lines 30-40).

With respect to claim 10, Rothbard et al. teaches a cationic polymer having 9 Arg residues (SEQ ID NO: 17).

With respect to claim 11, Rothbard et al. teaches a cationic polymer capable of enhancing the transport across a cell membrane (column 3, lines 17-25 and column 6, line 63-column 7, line 5).

With respect to claim 16, Rothbard et al. teaches a cationic polymer consisting of 6 to 25 contiguous Lys or Arg residues (SEQ ID NO:'s 2, 3-11 and 13-17).

With respect to claims 42 and 43, Rothbard et al. teaches a cationic polymer, which is not a tat peptide, comprising 5 to 25 contiguous Lys and/or Arg residues (SEQ ID NO:'s 1-17).

With respect to claim 44, Rothbard et al. teaches D-arginine (column 11, lines 49-50).

Mixson teaches the transport polymers can interact with an intracellular delivery component through non-covalent or covalent interactions (see entire document, particularly p14, lines 17-20).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ cationic polymers consisting of 5 to 25 contiguous Lys or Arg as taught by Rothbard et al. coupled to the semiconductor nanoparticles of Chan et al. in order to transport the semiconductor nanoparticle complex across the biological membrane. The advantage of using cationic polymers, which enhances the transport rate of the semiconductor nanoparticle complex across the biological membrane, provides the motivation to combine teachings of Chan et al. and Rothbard et al. since Chan et al. teaches cell-labeling using semiconductor nanoparticles via receptor-mediated endocytosis (p2018, 1st column) and Rothbard's

use of the cationic polymers would facilitate transport across the cell membrane in the endocytosis taught by Chan et al. Further, one of ordinary skill in the art would have had a reasonable expectation of success in employing a plurality of cationic polymers consisting of 5 to 25 contiguous Lys or Arg as taught by Rothbard et al. coupled to the semiconductor nanoparticles of Chan et al. since Rothbard et al. teaches that cationic polymers consisting of 5 to 25 contiguous Lys or Arg can be used for transport of conjugates across the biological membrane of eukaryotic and prokaryotic cells.

Further, because Mixson teaches that transport polymers can interact with an intracellular delivery component through non-covalent or covalent interactions, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute one means of binding the transport polymers to the intracellular delivery component for the other to achieve the predictable result of conjugating transport polymers to intracellular delivery components such as the semiconductor nanoparticles of Chan et al.

11. Claims 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018) in view of Rothbard et al. (U.S. Patent No. 6,495,663, filed on May 21, 1998) and Mixson (WO 01/47496 A1, published July 5, 2001 and filed December 20, 2000) as applied to claims 1, 10, 12, and 16 above, and further in view of Foster et al. (U.S. Patent No. 4,444,879, Apr. 24, 1984) and Boguslaski et al. (U.S. Patent No. 5,420,016, May 30, 1995).

Chan et al. in view of Rothbard et al. and Mixson teaches a semiconductor nanoparticle complex as set forth above. However, Chan et al. in view of Rothbard et al. and Mixson fails to teach that the semiconductor nanoparticle complex is in a kit with instructions for using the semiconductor nanoparticle complex.

Foster et al. teaches a kit comprising reagents for performing an assay and instructions for providing procedure for the use of the kit (see entire document, particularly column 15, lines 30-34).

Boguslaski et al. teaches that a test kit assembled by various system components for conducting assays is more convenient and facile for the test operator (see entire document, particularly column 7, lines 8-11).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to assemble the components of Chan et al. in view of Rothbard et al. and Mixson with instructions for providing procedure for the use of the kit as taught by Foster et al. in order to provide reagents in assembled components for conducting various assays. The advantage of assembling reagents in a kit, which makes its use more convenient and facile for a test operator as taught by Boguslaski et al., provides the motivation to combine teachings of Chan et al. in view of Rothbard et al. and Mixson and Foster et al. with a reasonable expectation of success. In addition, the advantage of giving instructions for performing the assay for the user provides the motivation for including instructions of Foster et al. in the composition of Chan et al. in view of Rothbard et al. and Mixson with a reasonable expectation of success as the

instructions would provide guidelines of how the assay should be performed for the user.

12. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al. (*Science*, 1998, Vol. 281, pp2016-2018) in view of Rothbard et al. (U.S. Patent No. 6,495,663, filed on May 21, 1998) and Mixson (WO 01/47496 A1, published July 5, 2001 and filed December 20, 2000) as applied to claim 1 above, and further in view of Szafranski et al. (U.S. Patent No. 5,681,745, Oct. 28, 1997)

Chan et al. in view of Rothbard et al. and Mixson teaches a semiconductor nanoparticle complex as set forth above. However, Chan et al. in view of Rothbard et al. and Mixson fails to teach that the semiconductor nanoparticle is coupled to streptavidin, avidin, or neutravidin, and the cationic polymer is coupled to biotin.

Szafranski et al. teaches that streptavidin, the preferred biotin-binding component, is a tetrameric protein, having four identical subunits, and is secreted by the actinobacterium *Streptomyces avidinii* (see entire document, particularly column 4, lines 9-28). Both streptavidin and its functional homolog avidin exhibit extremely tight and highly specific binding to biotin which is one of the strongest known non-covalent interactions between proteins and ligands (column 4, lines 9-28).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ biotin/avidin or biotin/streptavidin of Szafranski et al. as the non-covalent linkage in the semiconductor nanoparticle complex of Chan et al. in view of Rothbard et al. and Mixson (biotin or avidin/streptavidin on semiconductor

nanoparticle and avidin/streptavidin or biotin on cationic polymers) in order to take advantage of highly specific and extremely tight non-covalent interactions of biotin/avidin and biotin/streptavidin. The advantage of providing highly specific and extremely tight binding to cationic polymers to the semiconductor nanoparticles provide the motivation to combine teachings of Chan et al. in view of Rothbard et al. and Mixson and Szafranski et al. with a reasonable expectation of success.

Response to Arguments

13. Applicant's arguments with respect to claims 1, 3, 4, 6, 7, 10-13, 16, and 38-43 have been considered but are moot in view of the new ground(s) of rejection.

Applicant's argument that a person of ordinary skill in the art would not have been motivated to combine the teachings of Chan et al. and Rothbard et al. because the quantum dots of Chan et al. is entirely different from the conjugates disclosed by Rothbard et al. has been fully considered but is not found persuasive essentially for the reasons of record. Although it is acknowledged that the structures being transported in Chan et al. is entirely different from the conjugates of Rothbard et al., there is reasonable expectation of success in employing the transport polymers of Rothbard et al. for transporting the quantum dots across cellular membrane as the transport polymers conjugated to quantum dots would maintain their structural and functional characteristics as Chan et al. teaches that biomolecules can be immobilized on the quantum dot surface and maintain their structural and functional characteristics (see entire document). Therefore, there is a reasonable expectation of success that such

transport polymers bound to quantum dots would function substantially the same as the transport polymers bound to single molecules. Further, newly cited prior art, Mixon, set forth above teaches that transport polymers may be attached to intracellular delivery components such as liposomes, which would resemble the size of quantum dots. Given the teachings of Chan et al., Rothbard et al., and Mixon, one of ordinary skill in the art at the time of the invention would have been motivated to employ cationic polymers consisting of 5 to 25 contiguous Lys or Arg as taught by Rothbard et al. coupled to the semiconductor nanoparticles of Chan et al. in order to transport the semiconductor nanoparticle complex across the biological membrane. The advantage of using cationic polymers, which enhances the transport rate of the semiconductor nanoparticle complex across the biological membrane, provides the motivation to combine teachings of Chan et al. and Rothbard et al. since Chan et al. teaches cell-labeling using semiconductor nanoparticles via receptor-mediated endocytosis (p2018, 1st column) and Rothbard's use of the cationic polymers would facilitate transport across the cell membrane in the endocytosis taught by Chan et al.

Applicant's argument that a large number o cationic peptides attached by Chan et al.'s methods would likely not be suitable for transport into living cells because Rothbard et al. reports that conjugates containing too many cationic groups inhibit transport across cellular membranes has been fully considered. As stated by the applicant, too many cationic groups inhibiting transport across cellular membranes is well known in the art. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to optimize the number of cationic

polymers bound to the quantum dots of Chan et al., since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable range involves only routine skill in the art. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Applicant's argument that modifying the quantum dots of Chan et al. with the polycationic peptides of Rothbard et al. would produce a complex that will not be useful with viable cells because Rothbard et al. indicates that modifying Chan et al. to include multiple polymers being attached to the quantum dots would create a toxic product has been fully considered but is not found persuasive. Although it is acknowledged that certain cationic polymer composition may be toxic to cells, Rothbard et al. further teaches that use of naturally occurring L-amino acid residues in the transport polymers has the advantage that break-down products should be relatively non-toxic to the cell or organism (column 8, lines 26-36). Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to optimize the composition of cationic polymers to include a combination of different amino acids to render the final cationic polymer non-toxic to cells, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable range involves only routine skill in the art. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In view of the foregoing response to arguments, the all the prior art rejections set forth above have been maintained.

Since the prior art fulfills all the limitations currently recited in the claims, the invention as currently recited would read upon the prior art.

Conclusion

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to UNSU JUNG whose telephone number is (571)272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Unsu Jung/
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Patent Examiner
Art Unit 1641